

Recommendations from the 6th Advisory Committee on Safety of Medicinal Products (ACSoMP)

WHO Headquarters, Geneva, March 2009

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. Following is a summary of the recommendations from the Sixth Meeting.

Global Awareness of Medicine Safety

A CD-ROM is being prepared for different stakeholders in PV. The key message which is common for all is the concept of risk-benefit balance, and the fact that this can change as more information becomes available. As a new framework for action, three phases are proposed. Phase 1 is social marketing, phase 2 is identifying a medium for disseminating any developed messages, and phase 3 is creating social networking through patient's participation. Governments need to be made aware of this situation as well as the cost-effectiveness of having a PV system. Piloting the materials for the next stage of this work will help refine the key messages.

Recommendations/action

The Committee suggested that the CD-ROM should be piloted in order to assess its utility.

Developing a set of impact indicators specific to pharmacovigilance

Bench-marking and outcome assessment in pharmacovigilance was discussed in this session, which covered the rationale for PV indicators, broad and specific objectives, characteristics, types of indicators, data sources, and process of developing indicators. Structural indicators, process indicators and outcome (impact) indicators were discussed and the Committee agreed that both core and supplementary indicators should be developed.

Recommendation/action

A sub-group was assigned to continue developing a set of practical indicators for developing countries. A draft will be developed and discussed at the Annual Meeting of the National PV centres in Morocco in November. The final draft will be resubmitted to the next meeting of ACSoMP in 2010.

Developing a guideline for acute safety issues management

This session dealt with the management of acute safety issues by regulatory authorities. The major considerations were the evidence for decision-making after signal detection; analytical and methodological challenges; the optimal design and organization of a signal detection system; signal detection and public health; and risk communication. Several questions were posed including how people in developing countries react when regulatory decisions are made in developed countries with impact on their work; what is the basis of the decision and how do they prepare themselves for any potentially embarrassing public health crisis? The International Programme on PV suffers if acute safety issues are not handled properly.

Discussion

There are two issues to be considered separately. One is how and when to take action on an acute drug safety issue and the other is communicating i.e. sharing of information when action is taken so that others can understand and make their own decision. There is a need for a protocol to help in dealing with acute safety issues taking into consideration the limitation of the WHO ICSR (Individual Case Safety Reports) database in providing all the needed information. WHO should provide some guidance. National governments and regional agencies also have to assume some responsibilities. Confidentiality agreements regarding information exchange could be made by all members of the WHO International Drug Monitoring Programme, rather than bilaterally or in specific regions. Members agreed that ACSoMP can take the lead in designing a protocol on how and when to take action relating to an acute drug safety issues. However, when it comes to information sharing between regulators, the appropriate forum is the International Conference for Drug Regulatory Authorities (ICDRA).

Recommendations/ action

A recommendation should be made from ACSoMP to the planning committee for the next ICDRA to include a session on information sharing between regulators. A guideline for the management of acute safety issues will be prepared.

The International Network of Safe Medication Practice Centres

The International Medication Safety Network (IMSN) is a growing network of countries that are working together to promote safe medication practices. The group representing the network presented a case on why PV centres should be concerned with medication error reports. Medication errors are a system issue, and involve different regulatory bodies. There may be a reluctance to report medication errors because of litigation and punitive measures. There is a need to create an environment that will encourage reporting to understand "what caused the error" and "how to prevent the error" rather than "who caused the error".

Recommendations/action

A training workshop and / or a group activity should be organized at the Annual meeting of national PV Centres in Morocco, to share common concerns and objectives, and to facilitate collaborations between IMSN and PV networks.

Collaboration with the Expert Committee on the Selection and Use of Essential Medicines

A comprehensive draft guideline on safety information to be included with an application for inclusion (or deletion) of a medicine to (from) the WHO Model List of Essential Medicines (EML) was presented in this session. It outlined the difficulties involved in writing a new safety guideline, the structure of the proposed guideline and typical shortcomings of current applications. General issues were also mentioned including sources of information, general advice on the handling of safety information, drug administration, adverse drug reactions (ADRs) and references. It was considered whether every application for inclusion of a medicine on the EML should be accompanied by a risk management plan for the medicine involved. If so, these risk management plans should include suggestions for the management of any adverse drug reaction already known to be associated with the use of the specific medicine. It was also suggested that Cohort Event Monitoring (CEM) studies should accompany the deployment of any new medicine being proposed for mass administration in order to ensure that potential problems are quickly identified before large numbers of people are affected.

Recommendations/action

The current applications do not contain sufficient information to provide an adequate safety assessment. The safety component of most applications submitted to ACSoMP for assessment meet neither the proposed guidelines nor the current requirements. There is a need to establish new guidelines for the safety review of EML applications, both for applicants and for reviewers. ACSoMP will provide guidance and leadership in the development and adoption of these guidelines. The principles of the new guideline on safety evaluation of products proposed for inclusion in the EML should be complete, up-to-date, thorough, and scientifically valid. These principles should be involved for all safety assessments for the EML. These views should be presented to the forthcoming meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines.

Opening access to signals

A paper was presented on opening the WHO ICSR database to the public and on the wider distribution of the 'Signal' document. In principle opening the WHO database to the public and consumers was agreed. However, the narrative should be excluded (in order to protect patient confidentiality) and a new caveat statement should be drafted. It was also agreed that publication in the scientific media was a way of promoting the PV activities spearheaded by WHO/UMC. The Committee also agreed that it would be acceptable to provide information with no narratives to academia to help with research provided there is declaration of interests and the usual caveats inserted. The paper will be revised accordingly and presented at the next meeting of the national PV centres. The subject of making the 'Signal' document more available will be discussed further.

A Global Strategy for best practice in pharmacovigilance

The broad outline of a global strategy for best practice in pharmacovigilance was presented. It is part of the overall WHO strategy for the next 5 years. The UMC 4-year plan should be aligned with it. The main objectives will be to provide an advocacy tool for stakeholders, to develop a plan for a health-systems approach to PV and to

build cost-effective PV systems with broad scope to respond to questions for several health areas. The Committee was requested to discuss specific strategy elements and help identify a core group to lead the development of the strategy.

Recommendations/action

A sub-group of ACSoMP will develop the document further. This will then be circulated to other members of the Committee before finalizing the paper for presentation at the National PV Centres Meeting in November.

Leishmaniasis

The safety monitoring of drugs used in the leishmaniasis elimination programme in India, Nepal and Bangladesh was described including the assessment of the risk of preventable ADRs using surrogate markers, risk minimization including use of checklists of precautions and contraindications, use of patient cards, training of health-care workers and supervision, analysis of ADRs, and evaluation of PV activity. There are serious safety concerns about miltefosine an important drug which brings tremendous advantage in controlling the disease. The disease control programmes should work closely with the PV people to develop risk management and risk minimization plans.

Chagas Disease

WHO activities in the area of Chagas disease were presented. In 2007, WHO and Bayer Healthcare agreed on distributing 500 000 tablets free of charge of nifurtimox per year for Chagas disease. Chagas disease, which used to be found only in Latin America, is now present in other regions of the world including Europe and the Western Pacific mainly because of population movement. For example, in 2008, around 150 patients were diagnosed in Geneva with Chagas disease in the period of six months. There are two drugs available for Chagas disease: nifurtimox and benznidazole, both developed in the 1960s. In Bolivia, deaths have been reported in children related to the wrong use of nifurtimox. For benznidazole, WHO is in contact with a public Brazilian laboratory Laboratório Farmacêutico do Estado de Pernambuco - LAFEPE, manufacturer of the drug. WHO is trying to assist with the distribution of benznidazole and nifurtimox, both of which are in the WHO Essential Medicines List.

Even though nifurtimox and benznidazole were developed in the 60s, the available information on their safety is limited. It is important not only to implement PV but also to consider what kind of operational research needs to be implemented to ensure the collection, analysis and dissemination of safety information on these products, to patients and to health-care providers alike. Further discussions are necessary to determine optimal PV systems in these settings.

Vaccines

A dedicated vaccine safety specialist has been appointed at the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) to strengthen the signal detection process and improve the tools used for reporting vaccines. Activities are being undertaken to address key safety challenges with new vaccines, i.e. quality of safety data in individual countries, capacity to respond to crises, and quality of data at "global level" for signal detection and risk assessment. These include routine capacity strengthening, developing a global crisis management plan and strengthening a Global Network for the Post-marketing Surveillance (PMS) of newly pre-qualified vaccines. The Global Network for PMS of newly pre-qualified vaccines will provide data for these pre-qualified vaccines and will support the vaccine prequalification system with safety data in the post-marketing phase.

Other collaboration of the WHO vaccines and medicines safety departments and the UMC includes the development of a vaccine dictionary (part of the WHO Drug Dictionary) and an ATC classification for vaccines. The Global Advisory Committee on Vaccine Safety (GACVS) continues to provide support and oversight on all activities related to vaccine safety and acts as an independent advisory committee to the WHO. A member of ACSoMP serves on GACVS to ensure collaboration and sharing of information.

Malaria

A presentation was made on the rationale and need for PV of ACTs, collaboration between the malaria and medicines safety programmes in WHO, challenges at country, regional and global levels, and the way forward. The move to deregulate ACT as over-the-counter (OTC) medicines (thereby removing a barrier to treatment access) is

a big challenge especially since home-based care is involved. The way forward is to promote risk management plans, to empower consumers, and to strengthen integration between PV and public health programmes.

The Affordable Medicines Facility for Malaria (AMFm) which seeks to lower the net cost of ACTs will expand availability to this effective treatment. This increase in availability should be accompanied by an expansion in the safety monitoring systems for these medicines in all settings and under all conditions of use. The first phase of the AMFm will be immediately rolled out in 11 countries, providing both a challenge and an opportunity to develop PV systems or to strengthen existing ones.

There are various initiatives by different organizations in the area of PV of antimalarials in particular, and tropical diseases in general. These activities should be coordinated and members suggested that WHO takes a leading role in coordinating these initiatives which involve several different players. ACSoMP should be informed of all the safety studies being undertaken so that it can provide independent scientific and technical advice to WHO and member countries. Future plans in WHO include a meeting with MMV (Medicines for Malaria Venture) and some other partners to try to develop a joint protocol and guidelines for the PV of antimalarials. Such joint meetings would ensure harmonization in the safety monitoring of antimalarials.

Recommendations/action

An ACSOMP member will help WHO by coordinating various ongoing initiatives in Africa.

HIV/AIDS

Methods to improve safety of antiretroviral medicines in the public health context, pharmacovigilance for ARVs including gaps and needs, and a pilot project for improving the safety of antiretrovirals (ARVs) were presented. There are different toxicities expected of drugs used for post-exposure prophylaxis of HIV and for drugs used in the management of patients living with HIV/AIDS. As more and more people stay on treatment, toxicities become an important issue to address. There is a need to identify the gaps in ART programmes including the need for additional definitions and newer methodologies for capturing data relating to toxicity on ARVs. Towards this, a pilot project that is being funded by the Bill and Melinda Gates Foundation will establish internationally agreed reporting tools, strengthen PV capacity in some countries, support key studies, and to coordinate the analysis of safety data on ARVs.

Discussion

Switching of patients from first to second line regimen has huge cost implications. The safety data on ARVs is very limited regarding second line regimen. For example, the pharmacokinetic details of protease inhibitors in children are not known. It is important to learn the reasons why patients are switched from first to second line ART. Subjective reasons possibly dominate the switching of patients and this must be avoided. Guidelines on management of adverse events and treatment limiting toxicities should be developed and disseminated to all countries. Given the issues of co-morbidity and drug interactions, collaboration with other programmes is important to ensure the safe use of ARVs.

Review of specific medicines - artesunate+amodiaquine (ASAQ)

Based on the paper 'draft proposal for action', the safety issues on ASAQ were discussed. A meeting with DNDI and Sanofi-Aventis had been held as a result of which a Risk Management Plan for ASAQ has been produced by Sanofi-Aventis. Sanofi-Aventis is currently carrying out studies in Cote d'Ivoire on the real-life safety of its fixed dose combination of ASAQ. The weakness of the Sanofi-Aventis study design was discussed by ACSoMP. It appears several groups are planning to undertake active PV but without good planning. There are difficulties in proper engagement of some of the key personnel and organizations. Other drugs administered at the same time as ASAQ should also be considered.

Recommendations/action

ACSoMP members will review the Risk Management Plans submitted by Sanofi-Aventis and offer suggestions to WHO. In addition, a Consultant, currently reviewing some adverse events reported with ASAQ, will be requested to write a paper outlining the safety profile of ASAQ.

PV in Drugs of Dependence

E-mail discussions had been carried out about the use of pharmacovigilance data for the assessment of dependence and abuse potential of drugs of dependence. It was concluded that PV is one tool out of many for evaluating drug dependence liability and that a distinction should be made between ADRs from clinical trials and spontaneous reporting; that terms should not be defined too exactly as various terms can exist in parallel; it was agreed that the DDD is the best standard to be used as the unit and it was agreed that various drug classes should be approached separately.

A presentation on “opioids, safety surveillance and risk management”, elaborating key challenges in the review of post-marketing safety information on opioids in the USA was also made. The challenges for drugs with abuse potential include the fact that we are not necessarily looking to identify something new. In addition quantifying the known adverse events including those which indicate abuse is very difficult. Geographic clustering of abuse and abuse potential may occur but reporting practices are variable. Many reports are based on active ingredients and not on specific products used. The intended patient is often not the person who experiences the harm. Understanding prescribing decisions is very hard in the post-approval setting. The number of persons at risk is often unknown. Information is not always available in a timely manner. There are also several important factors that are difficult to ascertain in spontaneous reports, including medication theft, overuse of prescribed medication, abuse/dependence/addiction, overdose, non-prescription use etc.

It is important to understand the abuse potential of new formulations. Definitions related to abuse potential should be broadened, to include also non-opioids. The legal classification for products is also an important issue to be tackled.

Hot topics of current interest

a) Dietary supplement

A dietary supplement has been associated with reports of serious adverse events. The product was sold for pain relief on the Internet. The Medical Products Agency (MPA) in Sweden has detected that the product contains nimesulide. Four cases of liver damages including one fatality were reported in Sweden in relation to the product. The MPA intends to seek information from the European Union (EU) about experience from other member countries. The information is available on the MPA website at www.mpa.se.

b) Intermittent Preventive Treatment of malaria in Infants (IPTi)

A brief summary on IPTi and the various policy processes was given. It was discussed whether ACSoMP should be involved in policy debates and assessment of safety in these areas. The absence of a strong input from the safety team on some of these issues came up for discussion.

Recommendations/action

ACSoMP, as set out in the terms of reference for this Committee, should take a lead in issues that have implications on the safety of medicines, to guide and advise WHO in these matters.

c) Update on Gardasil

An update on the safety issues of Gardasil was provided. GACVS has carried out a review of the safety of Gardasil but there is no evidence or etiological basis for any of the safety concerns highlighted. A knowledge of the background rates of the conditions involved will help. GACVS will revisit the issue. The whole Gardasil issue brings to the fore the importance of data and information sharing between regulatory authorities.

d) Rotavirus vaccine

Current issues related to rotavirus vaccine and reports of Kawasaki disease were presented. Three spontaneous reports of Kawasaki disease in Germany were reported in association with RotaTeq vaccine in 2008. The number of reported cases was not more than expected. Review of the cases does not suggest a causal relationship at present. No signal has yet arisen from post-marketing studies. It is important to highlight the wrong association of Kawasaki disease with rotavirus vaccine.

e) Cough and Cold preparations

The Medicines and Healthcare Products Regulatory Agency (MHRA) has reviewed antitussives, expectorants, decongestants and antihistamines. The data showed no robust evidence of efficacy. The expert advisory committee concluded that the risk benefit balance is unfavourable in children under six. The MHRA has taken

regulatory action to contraindicate OTC cough and cold medicines containing these ingredients in children under six years. In addition, certain combinations that are illogical have been contraindicated in children under 12. The assessment reports will be published on the MHRA website.

Ethics in observational studies

The need for code of ethics for epidemiological and observational studies is being recognized globally. There are few documents discussing ethics in PV. The CIOMS document and the Indian Council of Medical Research (ICMR) document identify risks of epidemiological or observational studies, such as preventive intervention being denied. In New Zealand, public health investigations approved by competent authority and post-marketing surveillances using spontaneous reporting and prescription event monitoring are exempt from review by the ethics committee, whereas the guidelines (Volume 9A) governing medicinal products in the EU recommends that non-interventional post-authorization safety studies should be referred to an ethics committee. According to ICMR, informed consent is waived for research on publicly available information, research on anonymized biological samples and others. Ethical committee approval should be sought in all settings especially for CEM in countries where there are vulnerable populations. Individual consent may not be necessary or possible. A guidance document on ethics is needed, one that takes into consideration national and even local issues – CIOMS has developed a document on this.

In preparing a study protocol, it is important to think ahead and decide what data will be collected, for how long and how the data will be used immediately and in the future. The assumption that something is “for the public health good” should not prevent investigators from seeking ethical approval.

Internet Connectivity in Africa

A presentation on the WHO initiative called Africa Health Infoway (AHI) was made. Improving internet connectivity in Africa is the objective. The expected deliverables include health facilities being able to have access to health information, telemedicine, eLearning, disease surveillance, etc. Since WHO does not have a mandate for establishing infrastructure for the internet, a collaboration has been initiated between WHO and the International Telecommunications Union to set this up. There are also partnerships with regional organizations like the African Union Commission through which funding is being sought from the EU and other donors.

Discussion

There are several initiatives aimed at improving IT infrastructure in Africa, including an initiative called telemedicine task force, which involves the European Space Agency, the EU, African Union, WHO and others. This initiative proposes the use of satellite technology for e-health. ACSoMP asked for updates on the progress of this work. ACSoMP also asked how it can play an advocacy role and whether a letter from the Committee will help in advocacy. The utility of this project need to communicated to senior management, policy makers, donors etc.

Recommendations/ action

WHO medicines safety unit will cooperate with Africa Health Infoway in the following ways.

- An advocacy letter from ACSoMP will be sent to the Programme
- The PV programme tools (VigiFlow and CEMFlow) will be incorporated into the AHI plan
- Priority list of countries (to be supported by this initiative) will be identified
- Promotion of Africa Health Infoway in all workshops

Review of existing definitions

There is a lot of support on the concept of reviewing the existing definitions in pharmacovigilance. This topic was discussed at the Annual Meeting of National Centres in 2008. Signals and Adverse Reactions/Adverse Events are top priorities. During the last year, the CIOMS Working Group on Signal Detections has been moving on with new definitions. There are many people engaged in revision of definitions. ACSoMP was requested to give a firm view and guidance on whether and how WHO should lead this activity.

Discussion

WHO should take this activity forward because it has the mandate and the convening capacity to coordinate activities for developing global norms and standards. But it will be important to have the various stakeholders on

board. Led by ACSoMP, the WHO Programme for International Drug Monitoring should prepare a set of definitions that are needed and relevant for the Programme.

Recommendations/ action

A concept paper will be drafted for the next Annual Meeting of National Centres in November. Uppsala Monitoring Centre will take the lead, supported by two other members of the ACSoMP.